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Combination Povidone-Iodine and Alcohol Formulations More Effective, More Convenient Versus Formulations Containing Either Iodine or Alcohol Alone

A Review of the Literature

Abstract

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Topical antiseptic formulations containing single active ingredients of alcohol and iodine are recognized by the Food and Drug Administration as “generally safe and effective” for “preparation of the skin prior to surgery” or “prior to an injection” including “catheter care, ostomy hygiene, and intravenous site preparation” (Federal Register, 1994). However, a synergistic effect results from the combination of ethyl or isopropyl alcohol and povidone-iodine. Because

each active ingredient has different modes of action and performance characteristics, these combination formulations are faster acting with a broader spectrum of antimicrobial activity than formulations containing povidone-iodine alone, and more persistent than formulations containing ethyl or isopropyl alcohol alone.

The Food and Drug Administration (FDA), in its tentative final monograph (TFM) entitled Topical Antimicrobial Drug Products for Over-the-Counter Human Use: Tentative Final Monograph for Health-Care Antiseptic Drug Products,¹ defines a patient preoperative skin preparation as “a fast-acting [rapidly kills microorganisms], broad-spectrum [kills a wide variety of microorganism species], persistent [suppresses regrowth of remaining microorganisms] antiseptic-

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containing preparation that significantly reduces the number of microorganisms on intact skin.”^{1(p31442)} The FDA recognizes “patient preoperative skin preparation” as a broad category that includes preparation of the skin before surgery and other applications such as skin prepping before injection, catheter care, and catheter insertion-site preparation. The TFM goes on to list those active ingredients that the agency recognizes as “generally safe and effective” (Category 1) for preparation of the skin before surgery, as follows:

- Ethyl alcohol or ethanol (EtOH; CH₃CH₂OH) 60% to 95%
- Isopropyl alcohol or 2-propanol (IPA; CH₃CHOHCH₃) 70% to 91%
- Iodine topical solution USP (aqueous), containing 1.8 to 2.2 g of iodine (I₂) and 2.1 to 2.6 g of sodium iodine (NaI) in each 100 mL of solution²
- Iodine tincture USP, essentially iodine topical solution, USP, in which half the water has been replaced with ethyl alcohol²
- Povidone-iodine (PVP-I) 5% to 10%, a solution of povidone-iodine containing 85% to 120% of the labeled amount of iodine (I₂)³

Because formulations containing Category 1 ingredients are recognized by the FDA as “generally safe and effective,” no agency approval is required before marketing. However, manufacturers are expected to have on file the test data described in the TFM demonstrating the safety, efficacy, and stability of their antiseptic products containing Category 1 ingredients. Formulations indicated for preparation of the skin before surgery containing ac-

tive ingredients other than those listed previously as Category 1 agents (eg, chlorhexidine gluconate) can be marketed in the United States only after approval is received from the FDA through the New Drug (NDA) or Abbreviated New Drug Application (ANDA) process.

In the United States, PVP-I has been the most widely used antiseptic for cleansing arterial catheter and central venous catheter insertion sites.⁴ Tincture of iodine, iodophors (which include PVP-I), and alcohol are among the Centers for Disease Control and Prevention’s Category 1A recommended antiseptics (strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies) for catheter-site care.⁵ The Infusion Nurses Society (INS) makes similar recommendations in the *Infusion Nursing Standards of Practice*.⁶ A survey of standard catheter dressing change tray manufacturers’ Web sites indicates that many practitioners commonly use IPA and PVP-I during the same dressing change procedure.⁷⁻¹⁰ When IPA and PVP-I are used sequentially, INS recommends using IPA followed by PVP-I during catheter dressing change procedures.⁶

Over the past two decades, a number of manufacturers have introduced formulations that combine povidone-iodine with either ethyl or isopropyl alcohol dispensed in a variety of delivery systems. Table 1 lists products currently on the market (see footnote to Table 1 regarding DuraPrep®). This review presents an evaluation of the available literature pertaining to the safety and efficacy of IPA and EtOH, PVP-I, and PVP-I in combination with IPA or EtOH for preparation of the skin before surgery and for other applications such as catheter care and catheter-site preparation.

TABLE 1
Combination Alcohol / Povidone-Iodine* Formulations

Manufacturer	Brand	% EtOH or IPA	% Povidone-Iodine	% Available Iodine	Currently Available Delivery Systems
3M	DuraPrep™	74% IPA (w/w) [†]	*	0.7%	6 and 26 mL “shoe polish”-type applicators
Aplicare	ExCel _{AP} ™	72% IPA (v/v) [‡]	7.5% (w/w) [†]	0.75%	Pre-impregnated triple swabsticks
Becton Dickinson	Persist™	70% EtOH (w/w) [†]	10% (w/w) [†]	1.0%	Pre-impregnated single and triple swabsticks
Cardinal Health	Prevail®	62% EtOH (v/v) [‡]	5% (w/w) [†]	0.5%	59 mL “shoe polish”-type applicator
Cardinal Health	Prevail Fx®	72.5% IPA (w/w) [†]	8.3%	0.83%	40 mL “shoe polish”-type applicator

DuraPrep™ is a trademark of 3M, St. Paul, MN

ExCel_{AP}™ is a trademark of Aplicare, Inc., Branford, CT

Persist™ is a trademark of Becton, Dickinson and Company, Franklin Lakes, NJ

Prevail® and Prevail-Fx® are registered trademarks of Cardinal Health, Inc., Dublin, OH

*DuraPrep actually contains an acrylate/PVP-I copolymer and therefore contains no “povidone-iodine.”

[†](w/w), weight of ingredient versus weight of overall formulation

[‡](v/v), volume of ingredient versus volume of overall formulation

- **MECHANISMS OF ACTION:
ADVANTAGES AND DISADVANTAGES**

Ethyl and Isopropyl Alcohol

Alcohol is thought to be the oldest antiseptic, with its use for treating wounds dating back to the first century.¹¹ It was used as a topical antiseptic in the 14th century,¹² and as a preoperative skin preparation and surgical scrub in the 19th century.¹¹ Considered in 1999 by the Centers for Disease Control as the most effective and rapid-acting skin antiseptic containing a single active ingredient,¹³ both ethyl and isopropyl alcohol are known to exhibit rapid, substantive, broad-spectrum antimicrobial activity against both gram-positive and gram-negative vegetative bacteria, as well as yeast, fungi, and some viruses.¹⁴⁻¹⁶

Isopropyl alcohol is reported to be more effective than ethyl alcohol.^{11,16} The predominant mode of action for both isopropyl and ethyl alcohol is dehydration, protein denaturation,^{11,14,15,17,18} and cell wall/cell membrane disruption, resulting in the release of intracellular components^{11,16} and eventual loss of cellular function. However, because of their rapid evaporation rate, the alcohols are not persistent.^{11,17}

Iodines and Povidone-Iodine

First discovered in its elemental form by Courtois in 1812, iodine has been used as a topical antiseptic since the mid-1800s.¹⁹ Of all the chemical species found in solutions studied, free molecular iodine or “free iodine” is the only species with a concentration proven to correlate with bactericidal activity.¹⁹ Whereas free iodine correlates with bactericidal activity, total iodine correlates with a given formulation’s capacity to kill bacteria.¹⁹

Iodine exhibits rapid, substantive, broad-spectrum antimicrobial activity against bacteria, viruses, and fungi¹⁹ by rapidly penetrating microorganisms¹⁹ and attacking groups within nucleotides (DNA), fatty acids,¹⁹ and thiol groups within proteins.¹⁹ Through oxidation of the thiol group within the amino acid cysteine, protein synthesis is disabled.¹⁹

Although aqueous and alcohol-based solutions (tinctures) have been used to reduce bacterial, fungal, and viral contamination of the skin for more than 150 years, they typically are more irritating and less stable than iodophors such as solutions of povidone-iodine.¹⁴ In povidone-iodine solutions, the polyvinylpyrrolidone polymer (or povidone) is complexed with iodine, acting as a reservoir for “free” iodine, the functionally active antimicrobial agent in these formulations.¹⁹

First introduced in the 1960s, iodophors are less irritating than tinctures and more stable than aqueous iodine

topical solutions.¹⁹ However, because of their aqueous nature, iodophors typically require a longer period to dry after application than tinctures. More importantly, although they demonstrate some level of persistence,¹⁹ povidone-iodine formulations may require several minutes to reach maximal antimicrobial effect, as evidenced by many manufacturers’ directions for use (depending on the intended use) indicating an application time of 3 to 5 minutes.

Combinations of Alcohol and Povidone-Iodine

The mechanisms of antimicrobial action for combination PVP-I and alcohol formulations are the same as those for their individual ingredients. Alcohol provides rapid bactericidal activity via protein denaturation, dehydration, interference with metabolism, and cell wall/cell membrane disruption, whereas PVP-I provides a more prolonged bactericidal effect via attacking groups within nucleotides, fatty acids, and thiol groups within proteins.

Studies have investigated combination PVP-I and alcohol formulations. However, the published literature must be evaluated with caution. The performance of antiseptic products is dependent on a number of important factors, specifically

- the chemical identity of the active ingredient(s) (eg, IPA, PVP-I, chlorhexidine gluconate [CHG]).
- the concentration of the active ingredient(s).
- the nature of the excipients in which the active ingredient(s) is (are) delivered. Many surfactants and emollients deactivate certain antimicrobial agents. Hence, the active ingredient(s) may not be as effective in formulations that contain these surfactants or emollients as in those that do not. Not all formulations containing the same active ingredient(s) at the same concentrations can be expected to perform the same.
- whether the product(s) tested is used according to the manufacturer’s recommended directions for use, specifically
 - the time the antiseptic formulation is in contact with the skin (ie, the application time).
 - the volume of solution applied per square inch or centimeter of prepped skin.
 - the manner in which the formulation is applied (eg, firm scrubbing vs gentle painting, back and forth motion vs circular motion).
 - the shape and abrasiveness of the delivery system (typically gauze or a foam sponge) used to apply the formulation to the skin.

Therefore, practitioners must be aware of how specific products (and active ingredients within specific products) are compared before drawing any meaningful conclu-

sions regarding their relative performance. For example, regardless of the active ingredients, “product A” can typically be demonstrated as superior to “product B” simply by extending the application time of “product A” and shortening the time of application for “product B.” Studies that use either the manufacturer’s directions for use or directions provided by a government body or professional association typically are the most meaningful. The results of studies that do not use recommended directions should be considered with more caution.

Caution must be exercised when results from different studies are compared. Even if the same fundamental methods are used (eg, efficacy criteria as described in the TFM), greater reductions can be achieved based simply on higher baseline counts of bacteria on subjects’ skin because, generally speaking, the higher the baseline count, the greater log₁₀ reduction will be achieved. If “product A” is tested during the summer months when baseline counts are typically higher, and those results are compared with those for “product B” tested during the winter when baseline counts are typically lower, it is entirely possible to get different results, even if “products A” and “product B” are the same product. The most reliable comparisons result when “product A” and “product B” are tested at the same time by the same research team with the same population of subjects.

Surgical-Site Preparation Studies

Gilliam and Nelson²⁰ compared reductions in bacterial counts for 60 patients prepped with either a traditional two-step method consisting of PVP-I scrub followed by PVP-I paint or a combination PVP-I and alcohol formulation. They found no significant differences, but they found the combination formulation to be “more convenient, easier to apply, less time consuming, and potentially less expensive”²⁰⁽²⁵⁸⁾ than the two-step method.

In a similar study, Howard²¹ compared a 20-minute preparation of a PVP-I scrub solution followed by PVP-I paint with a combination PVP-I and alcohol formulation. He found bacterial kill and infection rates to be better than, albeit statistically equivalent to, the rates for the combination formulation. Howard also found the combination formulation to be “easy to use, faster and considerably less mess than the traditional method, resulting in significant savings in operating room time.”

Using the efficacy criteria described in the TFM for patient preoperative skin preparation products, Jeng and Severin²² found that a combination PVP-I and alcohol formulation yielded passing results with only a 30-second application. Arata et al²³ compared a povidone-iodine alcoholic solution with a povidone-iodine aqueous solution and found the effectiveness (as expressed by the log₁₀ reduction of bacteria on subjects’ skin) to be significantly higher with the povidone-iodine alcoholic

solution (2.02) than with the povidone-iodine aqueous solution (1.17).

Injection-Site, Catheter-Site, and Venipuncture-Site Preparation Studies

Birnbach et al²⁴ compared PVP-I with a PVP-I and alcohol combination for skin disinfection before epidural catheter insertion in parturients. They found that the combination provided “a greater decrease in the number of positive skin cultures immediately after disinfection, as well as in bacterial regrowth and colonization of the epidural catheters.”

Felton and Wolosyn²⁵ found that the antimicrobial activity of a combination PVP-I and alcohol formulation persisted for 9 days after a 30-second application. In this study, persistence was measured and defined as bacterial counts not returning to a pretreatment baseline level while the skin was covered with a transparent semipermeable membrane dressing left in place for the entire 9-day period.

Although no significant differences in blood culture contamination rates were detected in a comparison of 10% PVP-I, 70% IPA, tincture of iodine, and a combination PVP-I and alcohol formulation, Calfee and Farr²⁶ reported that “there was some evidence suggesting greater efficacy among alcohol-containing antiseptics.” Their findings showed that the combination PVP-I and alcohol formulation resulted in the lowest blood culture contamination rate.

Parietnti et al²⁷ found the incidence of catheter colonization to be significantly lower among intensive care unit (ICU) patients treated with alcohol than among those treated with an aqueous povidone-iodine solution protocol. In a similar study, Ramakers et al²⁸ reported rates of central venous catheter colonization to be 35.8/1,000 catheter days for ICU patients treated with 10% povidone-iodine, as compared with 25.0/1,000 catheter days when a formulation containing 5% alcohol plus 5% povidone-iodine was used.

Advantages of Combination Alcohol and Povidone-Iodine Formulations

The alcohols are faster acting than PVP-I, as evidenced by shorter application times required with the combination than with PVP-I alone.^{25,29,30} However, the PVP-I component yields more persistence in activity over time.^{25,29,31} When combined, the resulting formulations are both faster acting than PVP-I alone and more persistent than alcohol alone. As a result, the combination is more effective than either ingredient alone and more convenient to use than the individual ingredients in series.

Formulations containing the combination of PVP-I and alcohol provide a number of additional advantages, specifically these:

- They are faster and easier to apply than formulations requiring the common two-step practice of preparing the skin before surgery, which typically first uses a PVP-I-based detergent scrub, followed by an additional PVP-I topical solution or “paint.” Similarly, they are faster and easier to apply than formulations requiring the common two-step practice of preparing the skin during central catheter dressing changes, which typically first uses three IPA-impregnated swabsticks followed by three PVP-I-impregnated swabsticks. Providing both PVP-I and either IPA or EtOH in the same formulation enhances procedural compliance by negating the possibility of applying the IPA and PVP-I-impregnated swabsticks in the wrong order, potentially resulting in increased infection rates.
- The overall procedure time is reduced because of faster drying times enabled by the presence of either IPA or EtOH.
- The staining characteristics of PVP-I allow for easier recognition of areas that have been prepped, as compared with clear formulations (eg, chlorhexidine gluconate, IPA). Unrelated to their antimicrobial characteristics, many combination PVP-I and alcohol formulations also contain acrylate, which serves to thicken the formulation and form a somewhat tacky, water-resistant film upon drying. This results in several additional advantages, specifically
 - improved adherence of incise drapes and transparent catheter-site dressings.
 - sustained exposure of the skin to iodine, inevitably resulting in more persistence (efficacy).
 - enhanced resistance to inadvertent removal by water or bodily fluids, inevitably resulting in more persistence (efficacy).
 - enhanced viscosity, facilitating application onto the skin and helping to decrease the chance of solution “runoff” and pooling under the patient.

Disadvantages of Combination Alcohol and Povidone-Iodine Formulations

Although combination PVP-I and alcohol formulations are associated with a very low incidence of adverse experiences,^{23,32,33} they have the following specific disadvantages:

1. As with any product containing a high concentration of alcohol, combination PVP-I and alcohol formulations are flammable. As a result, precautions must be taken to ensure that they do not come in contact with ignition sources.
2. Some patients are sensitive or allergic to iodine or the excipients typically included in iodine-contain-

ing antiseptics. Precautions must be taken to ensure that these patients are not exposed to combination PVP-I and alcohol formulations.

3. In some cases (eg, cosmetic surgery), staining of the skin is undesirable. In these cases, combination PVP-I and alcohol formulations should not be used.

• CONCLUSION

Effective skin antisepsis is critical in preventing surgical and indwelling catheter-site infection. A review of the literature indicates that formulations containing a combination of PVP-I and either IPA or EtOH provide important advantages over formulations containing either of these ingredients alone, including more rapid kill, enhanced persistence, and both speed and ease of use.

• RECOMMENDATIONS FOR FUTURE RESEARCH

The first formulation containing a combination of CHG and an antiseptically meaningful concentration ($\geq 70\%$) of alcohol (2% CHG, 70% IPA) was introduced in the United States in 2002 (ChloraPrep; Medi-Flex, Inc., Leawood, KS). It since has received much attention and acceptance. Although a number of published studies have reported enhanced efficacy, cost savings, or both with combination CHG and alcohol formulations, as compared with aqueous povidone-iodine formulations,^{34-36,37-39} no study has compared combination CHG and alcohol formulations with any of the combination PVP-I and alcohol formulations.

After a meta-analysis comparing chlorhexidine with povidone-iodine solutions, Chaiyakunapruk et al⁴⁰ stated that “only the subset analysis of the five studies that used alcoholic [chlorhexidine] solution produced a statistically significant reduction [versus povidone-iodine] in catheter-related bloodstream infection.”⁴⁰⁽⁷⁹⁷⁻⁷⁹⁸⁾ Although these authors went on to say that this observation may be attributable to inadequate statistical power, it is unclear how much of the superior efficacy shown by the chlorhexidine formulations evaluated was actually attributable to the presence of alcohol versus chlorhexidine. The importance of this question is further advanced by data submitted as part of the New Drug Application for the approval of ChloraPrep. The data showed that ChloraPrep, under test conditions prescribed by the TFM, generally did not have significantly greater efficacy than 70% IPA alone.^{41,42}

Alcohol clearly plays a significant role in the efficacy of both chlorhexidine- and PVP-I-based combination

formulations. As a result, it is possible that combination PVP-I and alcohol formulations perform as well as combination CHG and alcohol formulations in many, if not all, applications. Well-controlled studies are needed to test this hypothesis.

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